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| EXAMINER | |
|---|---|
| CHEN, STACY BROWN | |
| ART UNIT | PAPER NUMBER |
| 1648 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 01/29/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/817,164 | DE ROOIJ ET AL. | |
| | Examiner | Art Unit | |
| | Stacy B. Chen | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2-4,6,7,17,36 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6,7,17,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 18, 2008 has been entered. Claims 2-4, 6, 7, 17 and new claims 36 and 37 are pending and under examination.

### *Claims Summary*

2. The claims are drawn to a process for preparing at least one sample for a method of detecting and quantifying total HIV nucleic acid present in the sample, said process comprising:

a) administering at least 100 microliters of the sample to a piece of filter paper capable of absorbing the sample, wherein the absorption results in a at least one spot,
b) drying the filter paper,
c) excising the spot from the surrounding filter paper,
d) extracting nucleic acid from the at least one spot of the at least one sample with a chaotropic nucleic acid isolation solution,
e) detecting HIV nucleic acid of interest, if present, and
f) quantifying the total HIV nucleic acid of interest in the sample.

In some embodiments, at least 200 or at least 250 microliters of sample is administered to the filter paper. In other embodiments, at least two samples are administered to the filter paper. Specifically, a known amount of a reference nucleic acid is administered to the filter paper. The HIV nucleic acid is from HIV-1.

The subject matter of new claims 36 and 37 is drawn to the same invention as claims 2-4. The method of claim 36 detects RNA in a sample using a similar methodology (broader) as claims 2-4. The limitation of claim 37 requires that at least 500 microliters of sample be

administered to the carrier. The embodiment of claim 37 falls within the same subject matter as in claims 2-4.

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-4, 6, 7, 17, 36 and 37 are rejected under 35 U.S.C. 103(a) as being obvious over Cassol *et al.* (Journal of Clinical Microbiology, 1997, 35(11):2795-2801, "Cassol 1997") in view of Cassol *et al.* (*Mem. Inst. Oswaldo Cruz*, Rio de Janeiro, 1996, 91(3):351-358, "Cassol 1996") and Gillespie (US Patent 5,482,834). The claims are summarized above.

The Cassol 1997 disclosure is directed to the quantification of HIV-1 RNA from dried plasma spots (abstract). The plasma spots were aliquoted on filter paper and stored for as long as two weeks prior to analysis by PCR (abstract). The Cassol 1997 reference does not teach the use of at least 100 microliters of sample for a single spot, nor does the Cassol 1997 reference disclose the use of a chaotropic nucleic acid isolation solution for extracting nucleic acid from the sample.

However, the Cassol 1996 reference discloses a method for the direct automated sequencing of HIV-1 field isolates from dried blood collected on filter paper, described on pages 355-356. The method includes the collection of blood by venipuncture and application of approximately 2 milliliters (2000 microliters) to filter paper via drops. The filter paper is air dried for three hours and placed in individual envelopes for storage/shipment for as long as two

weeks (abstract). The samples are excised from the filter paper and further processed (page 351, second column, last partial sentence). It would have been obvious to detect total HIV-1 RNA, as taught by Cassol 1997, using the similar methods of the Cassol 1996 reference. The main difference is the amount of sample aliquoted onto the filter paper. Since the 2000 microliter spot was adequate for quantifying particular HIV nucleic acid of interest, it is expected to also be adequate for total HIV-1 nucleic acid quantification. Given the quantification of total HIV-1 RNA in the Cassol 1997 reference using 50 microliters, and the success of using 2000 microliters to also detect HIV-1 RNA (specific portions), one would reasonably expect that total RNA would be able to be quantified using either the 50 microliters or the 2000 microliters of sample. Given the finite number of choices (50 or 2000 microliters) that are both known to have predictable results (quantification of HIV-1 RNA, total RNA of interest), the invention as a whole would have been obvious.

Further, although the Cassol 1997 reference does not disclose the use of chaotropic nucleic acid isolation solution for extracting nucleic acid from the sample, Gillespie discloses the use of a chaotropic salt solution along with nucleic acid probes to improve hybridization of probes with their targets (abstract). Gillespie teaches that a chaotropic salt dissolves a biological source of RNA, such as cells and bacteria (col. 6, line 65 through col. 7, lines 1-13). The salts are also used to expose DNA from its sources (col. 8, lines 19-47). It would have been obvious to use the chaotropic salts suggested by Gillespie in the methods of Cassol. One would have been motivated to use the chaotropic salts to improve the hybridization in PCR probes to nucleic acid. One would have had a reasonable expectation of success that the use of a chaotropic salt solution along with nucleic acid probes would improve hybridization of probes with their targets

(Gillespie, abstract) in view of Gillespie's salts being useful in methods of detecting HIV nucleic acid in blood (Examples 16 and 17).

With regard to the limitation in claim 6 about the administration of at least two samples to the filter paper, this would have been an obvious embodiment given a desire to have more than one sample available to compare and re-test, if necessary. With regard to the limitation in claim 7 about the administration of a known amount of a reference nucleic acid to the filter paper, this is also an obvious embodiment in view of the need to have a control with which to compare the test samples. These steps do not render the main inventive concept patentably distinct from the prior art.

With regard to the particular amounts of sample administered to the filter paper (solid carrier), it would have been well within the ability of the ordinary artisan to select an appropriate amount of sample given the teachings of Cassol 1996. The optimization of sample size is routine in the art when the main teachings are already known. In this case, Cassol 1996 discloses the detection of HIV-1 RNA using a 2000 microliter sample. It is expected that that sample size, or any sample size less than that (between 50 to 2000 microliters) would be acceptable for quantifying RNA. Therefore, the invention as a whole would have been *prima facie* obvious to one or ordinary skill in the art at the time of the invention.

***Response to Arguments***

4. Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant notes that Cassol 1997 references the use of dried blood spots for characterizing the genotype of virus, and references Cassol 1996. Applicant asserts that

the Cassol 1997 reference acknowledges that the use of dried blood spots to quantify RNA is a novel use of the dried blood spots, and that it would not have been obvious to use the dried blood spots for quantification in view of the Cassol 1996 reference alone.

- In response, the Office acknowledges that the teachings of the Cassol 1996 reference alone do not motivate one of ordinary skill to use the dried blood spots for quantification of RNA. Thus, the combination of the Cassol 1997 reference with the Cassol 1996 reference in the obviousness rejection.

- Applicant argues that one would not have been motivated to combine the teachings of the Cassol references because of the differences between quantification of RNA and sequences of RNA. In the Cassol 1997 reference, RNA is quantified, which requires that the total amount of RNA in the sample remain intact. In the Cassol 1996 reference, RNA is sequenced, which does not require the total amount of RNA in the sample to remain intact, rather, RNA is allowed to be degraded as long as a sufficient amount of RNA remains intact for sequencing. Further, Applicant argues that the Cassol 1996 reference only teaches semi-quantitative detection of HIV-1 drug-resistance mutations, not an absolute nucleic acid amount. Applicant asserts that the conditions used in the Cassol 1996 reference are not the same as those that would be used for a total RNA quantification experiment. Applicant asserts that the method used in the Cassol 1996 reference could allow for the degradation of RNA as long as the semi-quantitative detection was possible, whereas a total RNA quantification would require essentially all RNA to remain intact.

- In response, the differences between quantifying RNA and sequencing RNA are well known to the ordinary artisan. By combining the teachings of Cassol 1997 and Cassol 1996, one of ordinary skill in the art would have been well aware of the differences between treating the samples for quantification versus sequencing.
- It would have been obvious to detect total HIV-1 RNA (the nucleic acid of interest), as taught by Cassol 1997, using the similar methods of the Cassol 1996 reference. The main difference is the amount of sample aliquoted onto the filter paper. Since the 2000 microliter spot was adequate for quantifying the particular HIV nucleic acid of interest, it is expected to also be adequate for total HIV-1 nucleic acid quantification.
- With regard to Cassol's semi-quantitative measurements, note that RNA was extracted from the entire dried blood spot, amplified and quantified. A ratio was not the only calculation determined, rather, the total nucleic acid content of HIV-1 RNA from the dried blood spot was determined (see page 2796, first column, "Measurement of HIV-1 RNA viral burdens".

• Applicant argues that the Cassol 1997 reference teaches away from the use of large volume samples by disclosing the possibility that samples with high copy numbers and large volumes may result in amplification reactions becoming saturated (page 2799). Applicant also asserts that as of the time of the priority date for the present application (2003), it was commonly taught in the art that only small volume samples of blood and plasma were suitable for quantification purposes because high amounts of body fluid were deemed unsuitable due to perceived inhibitory effects. Applicant notes that the Cassol 1997 reference acknowledges this teaching by reducing the HIV quantification

standard from 100 to 25 microliters, in order to compensate for the smaller 50 microliter specimens for the dried plasma spots. Applicant argues that based on the uncertainty of using larger samples, one would not have had a reasonable expectation of success.

- In response, while Cassol 1997 does hypothesize that the use of a smaller input size increases sensitivity of RNA quantification *when* high copy numbers are present, Cassol 1997 does not preclude the use of larger sample sizes generally. The reference does not teach that quantification cannot be accomplished when using larger sample sizes (with high copy numbers) rather, it is hypothesized to be a matter of sensitivity. Note that the asserted negative teachings regarding larger sample size in Cassol 1997 are limited to instances when high copy numbers are present. Thus, Cassol's suggestion that larger sample sizes may be less sensitive than smaller sample sizes is only with regard to a particular situation (*i.e.*, high copy numbers present).
- Further, Cassol's adjustment of the QS from 100 to 25 microliters was done to accommodate the smaller sample size for the dried blood spot; however, if a larger sample was used, the method of quantification would have been more than adequate to quantify, thus a reasonable expectation of success that larger samples can be used to quantify RNA. Notably, the claims only require the detection and quantification of HIV; there are no limitations regarding sensitivity of those steps or degrees of accuracy.

***Conclusion***

5. No claim is allowed.

All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had

been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B Chen/
Primary Examiner, Art Unit 1648